Amendments to the Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (original) A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:

determining a level and/or an activity of

(i) a transcription product of a gene coding for HIF3a, and/or

(ii) a translation product of a gene coding for HIF3a, and/or

(iii) a fragment, or derivative, or variant of said transcription and/or translation product,

in a sample obtained from said subject and comparing said level or said activity, or both said level and said activity of said transcription product and/or said translation product to a reference value representing a known disease status and/or to a reference value representing a known health status, and said level and/or said activity is varied or altered compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2. (original) The method according to claim 1 wherein said neurodegenerative disease is Alzheimer's disease.

3. (currently amended) A kit for diagnosing or prognosticating a neurodegenerative disease[[,]] ~~in particular Alzheimer's disease~~[[,]] in a subject, or determining the propensity or predisposition, or the risk of a subject to develop such a disease, said kit comprising:

[[(a)]] at least one reagent which is selected from the group consisting of

(i) reagents that selectively detect a transcription product of a gene coding for HIF3a and

(ii) reagents that selectively detect a translation product of a gene coding for HIF3a;

whereby the diagnosis or prognosis or determination of the risk to develop ~~Alzheimer's~~ said neurodegenerative disease is determined by the steps of

[[(i)]] (a) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for HIF3a, and

[[(ii)]] (b) comparing said level or activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for HIF3a to a reference value representing a known health status and/or to a reference value representing a known disease status, and said level, or activity, or both said level and said activity, of said transcription product and/or said translation product is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status.

4. (original) A genetically altered non-human animal comprising a non-native gene sequence coding for HIF3a, or a fragment, or a derivative, or a variant thereof.

5. (currently amended) The genetically altered non-human animal according to claim 4 wherein said non-human animal is a mammal[[,]] ~~preferably a rodent, more preferably a mouse, a rat or a guinea pig~~[[,]] or an invertebrate animal[[,]] ~~preferably an insect, more preferably a fly such as the fly Drosophila melanogaster~~.

6. (currently amended) The genetically altered non-human animal according to claim 4 ~~claims 4 and 5~~, wherein the expression of said genetic alteration results in said non-human animal exhibiting a predisposition to developing symptoms, and/or displaying symptoms of neuropathology similar to a neurodegenerative disease[[,]] ~~in particular symptoms similar to AD~~.

7. (currently amended) The genetically altered non-human animal according to claim 4 ~~claims 4 and 5~~, wherein the expression of said genetic alteration results in said non-human animal which has a reduced risk of developing symptoms similar to a neurodegenerative disease, ~~in particular a reduced risk of developing symptoms similar to AD~~ and/or which shows a reduction of [[AD]] said symptoms and/or which has no [[AD]] symptoms due to an effect caused by the expression of the gene used to genetically alter said non-human animal.

8. (currently amended) ~~Use of~~ A method of developing diagnostics and therapeutics to treat neurodegenerative diseases, comprising screening, testing, or validating compounds, agents, and modulators using the genetically altered non-human animal according to claim 4 ~~claims 4 to 7 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease~~.

9. (currently amended) A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) a gene coding for HIF3a, ~~and/or~~

(ii) a transcription product of a gene coding for HIF3a, ~~and/or~~

(iii) a translation product of a gene coding for HIF3a, ~~and/or~~ and

(iv) a fragment, or derivative, or variant of (i) to (iii).

10. (currently amended) ~~An assay~~ A method for screening for a modulator of neurodegenerative diseases, ~~in particular Alzheimer's disease~~[[,]] or related diseases or disorders of one or more substances selected from the group consisting of

(i) a gene coding for HIF3a, ~~and/or~~

(ii) a transcription product of a gene coding for HIF3a, ~~and/or~~

(iii) a translation product of a gene coding for HIF3a, ~~and/or~~ and

(iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) contacting a cell with a test compound;

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and

(d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances

in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

11. (currently amended) A method of screening for a modulator of neurodegenerative diseases, ~~in particular Alzheimer's disease~~[[,]] or related diseases or disorders of one or more substances selected from the group consisting of

(i) a gene coding for HIF3a, ~~and/or~~

(ii) a transcription product of a gene coding for HIF3a, ~~and/or~~

(iii) a translation product of a gene coding for HIF3a, ~~and/or~~ and

[[(v)]] (iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) [[or]] to (iv) in a matched control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which animal no such test compound has been administered;

(d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases or disorders.

12. (original) The method according to claim 11 wherein said test animal and/or said control animal is a genetically altered non-human animal which expresses the gene coding for HIF3a, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native HIF3a gene transcriptional control element.

13. (currently amended) An assay for testing a compound[[,]] ~~preferably for screening~~ or a plurality of compounds to determine the degree of binding of said compounds to a HIF3a translation product, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said HIF3a translation product, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable[[,]] ~~in particular a fluorescently labelled~~ compound or a plurality of ~~fluorescently labelled~~ detectable compounds to be screened for said binding to said plurality of containers;

(iii) incubating said HIF3a translation product, or said fragment, or derivative, or variant thereof, and said detectable[[,]] ~~in particular fluorescently labelled~~ compound or ~~fluorescently labelled~~ compounds;

(iv) measuring amounts of ~~preferably fluorescence~~ detectable compound or compounds associated with said HIF3a translation product, or with said fragment, or derivative, or variant thereof; and

(v) determining the degree of binding by one or more of said compounds to said HIF3a translation product, or said fragment, or derivative, or variant thereof.

14. (currently amended) ~~Use of~~ The method of claim 1, comprising determining a level and/or an activity of protein molecules of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, or SEQ ID NO. 5, said protein molecules being translation products of the gene coding for HIF3a, or fragments, or derivatives, or variants thereof[[,]] ~~as diagnostic targets for detecting a neurodegenerative disease, preferably Alzheimer's disease~~.

15. (currently amended) ~~Use of~~ The method of claim 10, wherein said screening is for a modulator of protein molecules of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, or SEQ ID NO. 5, said protein molecules being translation products of the gene coding for HIF3a, or fragments, or derivatives, or variants thereof, ~~as screening targets for reagents or compounds~~ wherein said modulator is a reagent or compound for preventing, or treating, or ameliorating a neurodegenerative disease[[,]] ~~preferably Alzheimer's disease~~.

16. (currently amended) ~~Use of~~ A method for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for HIF3a, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, or a fragment, or derivative, or variant thereof, ~~for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with said antibody~~[[,]] wherein an altered degree of staining,

or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell which relates to a neurodegenerative disease[[,]] ~~preferably to Alzheimer's disease~~.

17. (new) The kit of claim 3, wherein said neurodegenerative disease is Alzheimer's disease.

18. (new) The kit of claim 3, wherein said translation product is a protein molecule of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, or SEQ ID NO. 5, said protein molecule being a translation product of the gene coding for HIF3a, or a fragment, or derivative, or variant thereof.

19. (new) The genetically altered non-human animal according to claim 5 wherein said mammal is a rodent, mouse, rat or guinea pig and said invertebrate animal is an insect or a fly.

20. (new) The genetically altered non-human animal according to claim 19 wherein said fly is *Drosophila melanogaster*.

21. (new) The genetically altered non-human animal according to claim 6, wherein said neurodegenerative disease is Alzheimer's disease.

22. (new) The genetically altered non-human animal according to claim 7, wherein said neurodegenerative disease is Alzheimer's disease.

23. (new) The method of claim 8, wherein said neurodegenerative disease is Alzheimer's disease.

24. (new) The method of claim 10, wherein said neurodegenerative disease is Alzheimer's disease.

25. (new) The method of claim 11, wherein said neurodegenerative disease is Alzheimer's disease.

26. (new) The method of claim 11, wherein said screening is for a modulator of protein molecules of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, or SEQ ID NO. 5, said protein molecules being translation products of the gene coding for HIF3a, or fragments, or derivatives, or variants thereof, wherein said modulator is a reagent or compound for preventing, or treating, or ameliorating a neurodegenerative disease.

27. (new) The assay of claim 13, wherein said detectable compound is a fluorescently detectable compound.

28. (new) The method of claim 16, wherein said neurodegenerative disease is Alzheimer's disease.